REMARKS

This Amendment is in response to the Office Action, dated November 5, 2009 ("Office Action"). Claims 1, 4, 13, 16, 18, 22, and 34 are amended and claims 2-3, 14-15, 19-21, and 39-43 are canceled by virtue of the present amendment (claims 12, 17, 33, and 37 having been previously canceled). Claims 1, 4-11, 13, 16, 18, 22-32, 34-36, and 38 are pending. No new matter is added. Examination and allowance of pending claims in view of the ensuing remarks are respectfully requested.

Claims 1, 18, and 34 have been amended to indicate that the neural stem cells exhibit markers characteristic of a precursor for astrocytic differentiated neural stem cells, said markers comprising A2B5 astrocytic precursor marker, do not express excitatory amino acid transporter 1 (EAAT1), and do not express excitatory amino acid transporter 2 (EAAT2). They have also been amended to note the full name of CXCR4 and SDF-1. No new matter is added. Support for these amendments may be found throughout the specification and in canceled claims 2, 3, and 39-40, and 42-43.

Claim 13 has also been amended to indicate that the neural stem cells, for which expression levels are determined and assessed, exhibit markers characteristic of a precursor for astrocytic differentiated neural stem cells, said markers comprising A2B5 astrocytic precursor marker, do not express excitatory amino acid transporter 1 (EAAT1), and do not express excitatory amino acid transporter 2 (EAAT2), as well as to note the full name of CXCR4 and SDF-1. No new matter is added. Support for these amendments may be found throughout the specification and in canceled claims 14, 15, and 41.

Claims 4, 16, and 22 have been amended to adjust the claim dependency due to the cancellation of certain claims, and to recite that the cell "further" exhibits GFAP to improve the clarity.

In the Office Action, the Examiner withdrew the §112, first paragraph rejection. Applicants thank the Examiner for the withdrawal of this rejection.

Applicants note that claims 7 and 8, while indicated to be rejected in the Office Action Summary, were not specifically rejected in the Detailed Action. Applicants request clarification for the rejection of these claims. Otherwise Applicants will assume that this was an error by the Examiner.

Claims 1-3, 5, 6, 34-36, 38-40 and 43 are rejected under §102(b), as allegedly being anticipated by Lapidot *et al.* (U.S. Patent No. 7,101,708), as evidenced by Ratajczak *et al.* (LEUKEMIA, 18:29-40, October 2003) for reasons of record. The Examiner notes that the claims are directed to isolated neural stem cells and are further characterized by their properties noted in the claims. The Examiner states that the rejection over Lapidot *et al.* is based on its express, implicit and inherent disclosures. The Examiner argues that "where Applicant has claimed a composition of matter in terms of a property or characteristic and the composition of the prior art is identical or substantially identical in structure or composition but the characteristic is not explicitly disclosed by the reference, a *prima facie* case of either anticipation or obviousness has been established and the burden of proof rests upon the Applicant to demonstrate that the prior art does not necessarily or inherently possess the characteristics of Applicant's claimed product." The Examiner contends that Lapidot *et al.* discloses isolated CXCR4-expressing ("CXCR4+") progenitors and stem cells that are responsive to SDF-1. The Examiner further contends that Lapidot *et al.* discloses the use of stem cells expressing a heterologous gene for the treatment of malignancies. In addition, the Examiner relies upon Ratajczak *et al.* to assert that (1) hematopoietic stem cells inherently express early neural stem cell markers and specific markers characteristic of a precursor for astrocytic differentiation, and (2) the capability of differentiation in neural cell fates is an inherent feature of CXCR4+ hematopoietic stem cells, and (3) SDF-1 plays a key role in the differentiation of CXCR4+ stem cells for tissue/organ repair throughout the body. With respect to the canceled claims, this rejection is rendered moot. With respect to pending claims, Applicants respectfully traverse this rejection.

A claim is anticipated if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (MPEP §2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir.

1987)). With respect to inherency, the Examiner must provide rationale or evidence tending to show inherency. MPEP §2112(IV). "In relying upon the theory of inherency, the examiner must provide a basis in the fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP §2112(IV) (citing *Ex parte* Levy, 17 USPQ2d 1461, 1464 (BPAI 1990). "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP §2112(IV) (emphasis in original) (citing *In re* Rijckaert, 9 F.3d 1531, 1534 (Fed. Cir. 1993)). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" MPEP §2112(IV) (emphasis added) (citing *In re* Robertson, 169 F.3d 743, 745, 49 USPQ 2d 1949, 1950-51 (Fed. Cir. 1999)). When the basis for a rejection is a reference teaching a product that appears substantially identical to the claimed product, the burden shifts to an applicant to show an unobvious difference **only after the examiner presents evidence to show inherency**. MPEP §2121(V).

The Examiner has not shown that the prior art cells are the same or substantially similar to the claimed cells.

Applicants respectfully remind the Examiner that claim 1 is directed to an isolated neural stem cell exhibiting a CXCR4 receptor, demonstrating an affinity for the chemokine SDF-1, exhibiting markers characteristic of a precursor for astrocytic differentiated neural stem cells, said markers comprising A2B5 astrocytic precursor marker, not expressing EAAT1, and not expressing EAAT2; and claim 34 is directed to a kit comprising a population of these isolated neural stem cells. As discussed in the specification, "the absence of EAAT1/EAAT2 expression in [tumor tropic NSC populations], in conjunction with expression of A2B5 and clear absence of fully differentiated morphology, indicate that tumor tropic cell populations are comprised of progenitor cells that had initiated, but not completed, pathways towards astrocytic

differentiation." (Specification page 23, particularly, lines 14-19.) Applicants have identified a subtype of neural progenitor cells that are tumor tropic.

Applicants submit that the Examiner has overlooked the fact that the composition of the prior art (Lapidot *et al.*) and the claimed composition are not "identical or substantially identical in structure or composition" as alleged by the Examiner. The Examiner has cited prior art relating to hematopoietic stem cells. Applicants' claims are directed to neural stem cells. One of ordinary skill in the art will readily appreciate that neural stem cells and hematopoietic stem cells, while sharing several cell markers, are not identical or substantially identical. Applicants respectfully remind the Examiner that the claims are not merely directed to "stem cells" expressing or not expressing certain cell markers. The claims are directed to neural stem cells expressing certain cell markers and not expressing certain cell markers. That is, the claims are directed to a particular subtype of neural stem cells. The descriptor "neural" imparts structural features on the stem cells that one of ordinary skill in the art will readily appreciate are different from the structural features that the descriptor "hematopoietic" would impart on stem cells. The Examiner has even acknowledged that the claims are directed to isolated neural stem cells (Office Action, page 3, last paragraph); that is, the stem cells are characterized as being neural stem cells. The Examiner admits that the [neural stem] cells are further characterized by their properties. The Examiner also admits that Lapidot *et al.* discloses hematopoietic stem cells (Office Action, page 4, second full paragraph). Accordingly, the Examiner has erroneously alleged that the prior art composition and the claimed composition are identical or substantially identical. They may share some characteristics, but the descriptor of neural and hematopoietic clearly distinguishes the two different cell types. Furthermore, the expression of markers indicative of a precursor for astrocytic differentiated neural stem cells, including A2B5 astrocytic precursor marker further distinguishes the neural stem cells from hematopoietic stem cells. Since the cells are different, the Examiner has not met her burden of showing that the cells are substantially identical.

The Examiner has not presented any evidence or reasoning tending to show inherency.

Even if the prior art cells and the claimed cells are substantially identical, which Applicants in no way concede, the Examiner still has the burden of presenting evidence or reasoning to show the alleged inherent features. MPEP §2112(V). The Examiner cannot merely rely on an assertion that the cells are substantially identical and attempt to pass the burden to Applicants.

The Examiner must show that the cells described by Lapidot *et al.* are neural stem cells that express markers indicative of a precursor for astrocytic differentiated neural stem cells, including A2B5 astrocytic precursor marker, that do not express EAAT1, and that do not express EAAT2. Identifying a possibility or a probability of Lapidot *et al.*'s cells having these characteristics is unmistakably not enough. The Examiner must provide evidence or reasoning tending to show that Lapidot *et al.*'s cells **necessarily** have these characteristics.

In the interest of advancing prosecution and in no way conceding to the merits of the Examiner's reason for rejection, claims 1 and 34 have been amended to unequivocally convey that a neural stem cell is selected and is encompassed by the claim. The selection of the neural stem cell clearly imparts structural features regarding the neural stem cell that distinguishes the claimed neural stem cell from other stem cells that may also exhibit a CXCR4 receptor and demonstrate an affinity to SDF-1. Further, the neural stem cell is further identified by its expression of markers indicative of astrocytic differentiated neural stem cells, including A2B5 astrocytic precursor marker, and by its lack of expression of EAAT1 and EAAT2. Claims 1 and 34 and their dependent claims are not claiming hematopoietic stem cells.

Applicants submit that the Examiner's allegations regarding Ratajczak *et al.* is mistaken. Ratajczak *et al.* does **not** show that hematopoietic stem cells inherently express early neural stem cell markers or specific markers characteristic of a precursor for astrocytic differentiation. Ratajczak *et al.* notes that bone marrow-derived hematopoietic stem cells have been suggested to transdiffferentiate into tissue-specific stem cells. (See Ratajczak *et al.*, Abstract.) In other words, the tissue-specific stem cells may have at one point in time been hematopoietic stem cells, but the hematopoietic stem cells have transdifferentiated into cells of a more committed state.

These tissue-specific stem cells are **not** the same as hematopoietic stem cells even though they may have originated from hematopoietic stem cells. The Examiner's apparent allegation that the tissue-specific stem cells noted by Ratajczak *et al.* are the same as hematopoietic stem cells is analogous to alleging that a fully committed brain cell is identical to an embryonic stem cell. Clearly, this is not correct. Furthermore, Ratajczak *et al.* describes the use of "freshly isolated cells to **exclude** the potential for 'transdifferentiation' of hematopoietic stem or mesenchymal cells." (See Ratajczak *et al.*, Abstract; emphasis added.) The freshly isolated cells are peripheral blood mononuclear cells, in which the early markers for neural cells were detected. Ratajczak *et al.* does not disclose any detection of early markers for neural cells in the hematopoietic stem cells. While Ratajczak *et al.* teaches that CXCR4 positive cells express neural markers, these CXCR4 positive cells are peripheral blood mononuclear cells; they are not hematopoietic stem cells and not neural stem cells. Consequently, Ratajczak *et al.* does not provide evidence that hematopoietic stem cells inherently express early neural stem cell markers or specific markers characteristic of a precursor for astrocytic differentiation. Consequently, a *prima facie* case of inherent anticipation has not been established by the Examiner and the burden of showing that the prior art cells do not possess the characteristics of Applicants' claimed neural stem cells has not passed to Applicants.

The Examiner has not made a prima facie case of anticipation or inherent anticipation.

In sum, Lapidot *et al.* does not teach identical or substantially identical cells to the ones that are currently claimed. Ratajczak *et al.* does not provide any evidence that hematopoietic stem cells inherently express early neural stem cell markers, or specific markers characteristic of a precursor for astrocytic differentiation. Ratajczak *et al.* cannot be relied on for the teachings that are alleged by the Examiner. Accordingly, Lapidot *et al.* as allegedly evidenced by Ratajczak *et al.* does not anticipate claims 1, 5, 6, 34-36, and 38. In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner rejects claims 1-3, 34, 39, 40, and 43 under §102(b), as allegedly being anticipated by Lazarini *et al.* (EUROP J OF NEUROSCI, 12:117-125, 2000) for reasons of record. In particular, the Examiner alleges that Lazarini *et al.* teaches neural progenitor cells that are CXCR4+, responsive to SDF-1, and exhibit markers that are characteristic of a precursor for astrocytic differentiation. The Examiner asserts that while Lazarini *et al.* does not characterize the cells as exhibiting the A2B5 marker or not expressing EAAT1/EAAT2, the cells of the prior art and the cells of the present invention are substantially identical and therefore the properties are merely inherent features. Again, the Examiner asserts that the burden of proof rests upon Applicants to demonstrate that the prior art does not necessarily or inherently possess the characteristics of Applicants' claimed product. With respect to the canceled claims, this rejection is rendered moot. With respect to the pending claims, Applicants respectfully traverse this rejection.

As explained above, the prior art cells and the claimed cells are not substantially identical. Even if the prior art cells and the claimed cells are substantially identical, which Applicants in no way concede, the Examiner still has the burden of presenting evidence or reasoning to show the alleged inherent features. MPEP §2112(V). The Examiner cannot merely rely on an assertion that the cells are substantially identical and attempt to pass the burden to Applicants.

Applicants again remind the Examiner that claim 1 is directed to an "isolated" neural stem cell that expresses markers indicative of a precursor for astrocytic differentiated neural stem cells, including A2B5 astrocytic precursor marker, and does not express EAAT1 and EAAT2. Similarly, claim 34 is directed at a kit comprising isolated neural stem cells with these characteristics. As discussed above, Applicants have identified a subtype of neural progenitor cells that are tumor tropic.

Lazarini *et al.* discusses neurons and astrocytes. The claims are directed to isolated neural stem cells, not differentiated (i.e., committed) neural cell types. Further, the claimed isolated neural stem cell's lack of expression of EAAT1 and EAAT2 indicates that the cell is not yet an astrocyte. (See e.g., specification, page 23, lines 5-10.) With respect to Lazarini *et al.*'s general disclosure that neuronal progenitors expressed CXCR4 and migrated towards SDF-1, Lazarini *et al.* did not recognize that

there is a subtype of neural stem cells that express CXCR4, that demonstrate an affinity towards SDF-1, that express markers indicative of a precursor for astrocytic differentiated neural stem cells, including A2B5 astrocytic precursor marker, and that do not express EAAT1 and EAAT2. Assuming arguendo that Lazarini *et al.*'s studied population of neural progenitor cells may have contained neural stem cells that do not express EAAT1 or EAAT2 (although Applicants do not suggest that this assumption is true and do not concede that this assumption is true, and it is still the Examiner's burden to present evidence or reasoning tending to show that this is necessarily true), there was no recognition of this subtype of neural stem cells by the prior art and thus, there cannot be any recognition of its benefit. Accordingly, there would be no reason in the prior art to isolate this subtype of neural stem cells. Applicants have recognized this subtype of neural stem cells and determined that this subtype of neural stem cells are tumor tropic and thus, are claiming the isolated subtype of neural stem cells. Applicants are not claiming the same general population of the neural progenitor cells discussed in Lazarini *et al.* Accordingly, Lazarini *et al.* does not anticipate claims 1 and 34. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner rejects claim 9 as being allegedly unpatentable under §103(a) based on Lapidot *et al.* as applied to claims 1-3, 5, 6, 34-36, 38-40, and 43, in view of Tahara *et al.* (CANCER RESEARCH (1994), 54:182-189) for reasons of record. Particularly, the Examiner again asserts that the product of the claims is identical or substantially identical to those disclosed by Lapidot *et al.* The Examiner further asserts that Lapidot *et al.* teaches methods for the expression of heterologous genes and Tahara *et al.* teaches that it is known in the art to engineer cells to secrete IL-12 to suppress tumor growth *in vivo*. Thus, the Examiner maintains that the invention as a whole is prima obvious. Applicants respectfully traverse this rejection.

Applicants submit that claim 9 is not rendered obvious by Lapidot *et al.* in view of Tahara *et al.* under §103(a). As discussed above, Lapidot *et al.* does not disclose cells that are identical or substantially identical to those that are claimed in claim 1, through which claim 9 is dependent. Lapidot *et al.* discloses hematopoietic stem cells, not neural stem cells. The Examiner also has not presented any evidence or rationale

tending to show that cells necessarily possess the characteristics that are claimed. Showing that hematopoietic stem cells may express early neural stem cell markers, or specific markers characteristic of a precursor for astrocytic differentiation would not show that the cells described by Lapidot *et al.* anticipate the claimed invention because the claim is unequivocally directed to neural stem cells. Further, Ratajczak *et al.* does not provide any evidence that hematopoietic stem cells inherent express early neural stem cell markers, or specific markers characteristic of a precursor for astrocytic differentiation, or that the cells do not express EAAT1/EAAT2. Ratajczak *et al.* cannot be relied on for the teachings that are alleged by the Examiner because the Examiner has mistaken the disclosure by Ratajczak *et al.*

The Examiner is again ignoring the fact that neither Tahara *et al.* nor Lapidot *et al.* provides sufficient detail to achieve the present invention of CXCR4+ neural stem cells heterologously expressing IL-12. In Lapidot *et al.*, the CXCR4+ stem cells are hematopoietic cells, unlike the neural stem cells of the instant application. There is no teaching of using a neural stem cell. Even if the combination of Tahara *et al.* and Lapidot *et al.* is appropriate, which Applicants do not concede, the combination does not teach neural stem cells expressing IL-12 as required by claim 9. Thus, the combination of Tahara *et al.* and Lapidot *et al.* cannot render claim 9 obvious if it does not teach or suggest all the elements of the claim. In light of the foregoing, Applicants request withdrawal of the rejection under 35 U.S.C. §103(a).

//...p. 16.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 633-6800 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
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